SEQ ID NO: 4 and International Protein Index accession number IPI00044749.2 annotated as *Homo sapiens* (Human) SERINE/THREONINE KINASE NEK-1; as **Exhibit D**, an abstract by Letwin, et al., entitled "A mammalian dual specificity protein kinase, Nek1, is related to the NIMA cell cycle regulator and highly expressed in meiotic germ cells" (EMBO J, Oct;11(10):3521-31, 1992); as **Exhibit E**, an abstract by Upadhya, et al. entitled "Mutations in a NIMA-related kinase gene, Nek1, cause pleiotropic effects including a progressive polycystic kidney disease in mice" (Proc Natl Acad Sci USA, Jan 4;97(1):217-21, 2000).

AMENDMENT

In the claims:

Please cancel claims 1-3, 6-10, without prejudice and without disclaimer, as being drawn to an non-elected invention. Please add new claims 11-14.

11.(New) An expression vector comprising a nucleic acid sequence of Claim 4.

12.(New) A cell comprising the expression vector of Claim 11.

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13.(New) An expression vector comprising a nucleic acid sequence of Claim 5.

14.(New) A cell comprising the expression vector of Claim 13.

RESPONSE

I. Status of the Claims

Claims 1-3, 6-10 have been canceled as being drawn to an non-elected invention without prejudice and without disclaimer. New claims 11-14 have been added. Claims 4, 5, and 11-14 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Claims

New claims 11 and 13 have been added to more clearly claim certain aspects of the invention. Claims 11 and 13 find support throughout the specification as originally filed, with particular support being found at least at page 13, lines 6-13.

New claims 12 and 14 have been added to more clearly claim certain aspects of the invention. Claims 11 and 13 find support throughout the specification as originally filed, with particular support being found at least at page 13, lines 13-19.

As new claims 11-14 are fully supported by the specification and claims as originally filed and as such do not constitute new matter. Entry therefore is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects claims 4 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully traverse.

The present application describes human kinases, in particular variants of human NEK-1, a dual specificity kinase that participates in different signaling pathways to regulate diverse cellular processes and identified a role for Nek1 in the kidney and open a new avenue for studying cystogenesis. Therefore, a preponderance of the evidence clearly weighs in favor of Applicants' assertion that the presently described sequences have a specific, credible, and well-established utility.

The Examiner seems to be requiring that Applicant provide particular data. However, as stated above in *Brana*, the Federal Circuit has clearly stated that this is not the standard for utility under 35 U.S.C. § 101. The Examiner states that a "real-world" utility does not require further research (Action at page 5). However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not

"experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that to violate § 101 the claimed invention "must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985)) states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Id* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Action recognizes that the specification teaches that the proteins of the present invention are kinases.. As the protein of the instant invention belongs to a family of compounds with a common, well established specific and substantial utility, the Federal Circuit's ruling in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is completely on point. In *Brana*, the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted.

As just <u>one</u> example of utility of the present nucleotide sequences, Applicants point out that, as taught in the specification as originally filed, at least at page 8, the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Evidence of the "real world" <u>substantial</u> utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transaction was $620 million) that it was acquired by large pharmaceutical company, Merck & Co., for significant sums of money. The "real world" <u>substantial</u> industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established.

The sequences of the present invention describe a metalloprotease and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encodes a human kinase, as detailed throughout the specification it is a human homolog of the mouse NEK-1 protein, a dual specificity kinase that has a role in cell cycle regulation. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of the Venter *et al.* article (Science, 2001, *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequences

define biologically validated sequences that provide a unique and specific resource for mapping genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

As evidence of the credibility of Applicants assertion that the present invention is a human kinase, in particular variants of human NEK-1. Applicants submit results of a BLASTP analysis comparing SEQ ID NO: 4 and International Protein Index accession number IPI00044749.2 annotated by third party scientists, wholly unaffiliated with Applicants, as *Homo sapiens* (Human) SERINE/THREONINE KINASE NEK-1. This analysis indicates that these two proteins share a greater than 89% identity (the query sequence marked by Xs were masked by the BLAST program). NEK-1 is known to the art, see for example, Letwin, et al., "A mammalian dual specificity protein kinase, Nek1, is related to the NIMA cell cycle regulator and highly expressed in meiotic germ cells", EMBO J, Oct;11(10):3521-31, 1992, abstract presented as **Exhibit D**).

Studies in homozygous NEK-1 mutant animals indicated pleiotropic phenotypes that suggest that the NEK1 protein participates in different signaling pathways to regulate diverse cellular processes

and identified a role for Nek1 in the kidney and open a new avenue for studying cystogenesis and identifying possible modes of therapy (Upadhya, *et al.*, "Mutations in a NIMA-related kinase gene, Nek1, cause pleiotropic effects including a progressive polycystic kidney disease in mice", Proc Natl Acad Sci USA, Jan 4;97(1):217-21, 2000: abstract presented as **Exhibit E**). This reference clearly supports Applicants' position that the invention has utility and a known disease association.

Given this clear and convincing evidence that those of skill in the art would recognize the present invention as a kinase, more specifically A NEK-1, whose function and disease association are described in, among others, the citations whose abstracts are shown in **Exhibit D** and **Exhibit E**. Clearly, there can be no question that Applicants' asserted utility for the described sequences is "credible." Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode a kinase, more particularly that of NEK-1 and has all the recognized uses thereof. In contrast, the Examiner has provided no evidence of record indicating that those of skill in the art would not recognize the sequences of the present invention encode a kinase, specifically NEK-1. As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35 U.S.C. § 101, and the Examiner's rejection should be withdrawn.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. The PTO has issued numerous patents on polynucleotide sequences that have not been directly shown to be associated with the function of the protein that is set forth in the specification, or a direct association between the claimed sequences and a particular "disease or condition" (Action at page 3), the conditions apparently set forth by the Examiner as allegedly necessary to comply with 35 U.S.C. § 101. The Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,2812 (each of which claims short polynucleotide fragments), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples). None of these issued U.S. Patents contain examples of the "real-world" utilities that the Examiner seems to be requiring in the present Action. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section V below), Applicants submit that the presently claimed polynucleotide must also meet the requirements of

35 U.S.C. § 101.

For each of the foregoing reasons, Applicants submit that the present invention is supported by a specific, substantial, and credible utility that is well-established, therefore the rejection of claims 4 and 5 under 35 U.S.C. § 101 has been overcome, and respectfully request that the rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-3 have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV above. Applicants therefore respectfully request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing amendments and remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Ramirez have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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